REMARKS

Reconsideration of the above-identified application in view of the amendment above and the remarks below is respectfully requested.

Claim 56 has been canceled in this paper. Claims 1, 11, 34-41 and 49-55 have been amended in this paper. No new claims have been added in this paper. Therefore, claims 1-11, 34-41, 42-55 and 57-63 are pending and are under active consideration.

Claims 34-41 and 49-56 stand rejected under 35 U.S.C. 112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." In support of the rejection, the Patent Office states the following:

> Claims 34-41 and 49-56 provides for the use of deuterated catecholamine derivatives, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Insofar as the subject rejection pertains to claim 56, the rejection is moot in view of the cancellation herein of claim 56. Insofar as the subject rejection pertains to claims 34-41 and 49-55, Applicant has rewritten these claims so that they are no longer "use" claims, but rather, are "method" claims that recite an active, positive step. Accordingly, the rejection has been overcome and should be withdrawn.

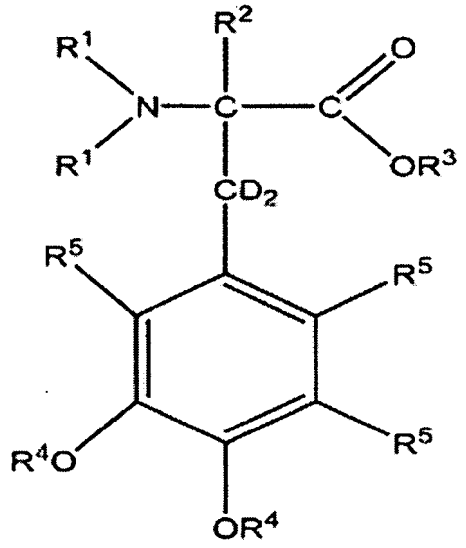
Claims 34-41 and 49-56 stand rejected under 35 U.S.C. 101 "because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for

example *Ex parte Dunki*, 153 USPQ 678 (Bd. App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966)."

For at least the reasons stated in connection with the previous rejection, the subject rejection should be withdrawn.

Claims 1, 2, 9 and 10 stand rejected under 35 U.S.C. 102(b) "as being anticipated by Bennett et al (J. Chem. Soc. (C), 1970, page 2049-2051)." In support of the rejection, the Patent Office states the following:

> The instant claims are directed to deuterated catecholamine derivatives of the general formula I as embodied in claim 1, 2, 9 and 10 where the β-carbon is dideuterated as shown.

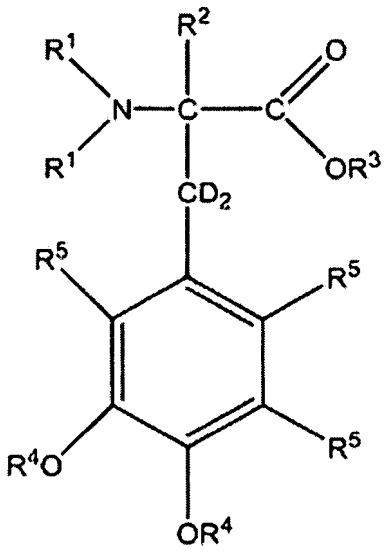


Formula I

> Bennett et al disclose (see column 1, 2nd para, page 2050, J. Chem. Soc. (C), 1970, page 2049-2051) 3,4-dihydroxy [β-$^{2}H_2$]phenylalanine, thus anticipating the instant claims.

Applicant respectfully traverses the subject rejection. Claim 1, from which claims 2, 9 and

10 depend, has been amended herein and now recites "[d]euterated catecholamine derivatives of the general formula I



Formula I

wherein

R^1 is H or D, R^2 indicates H or D, R^3 is H, D, C_1-C_6 alkyl or C_5 to C_6-cycloalkyl, deuterated C_1 to C_6-alkyl or deuterated C_5 to C_6-cycloalkyl, R^4 indicates H or D and R^5 is H or D, and wherein at least one of R^1, R^2, R^3 and R^4 is D."

Thus amended, claim 1 is neither anticipated by nor rendered obvious over Bennett et al. for at least the reason that Bennett et al. fails to teach or to suggest a deuterated catecholamine derivative as claimed in claim 1. In particular, whereas the deuterated catecholamine derivative of claim 1

requires, amongst other things, **that at least one of R^1, R^2, R^3 and R^4 be D**, the mere disclosure in Bennett et al. of 3,4-dihydroxy [β-$^2H_2$] phenylalanine provides no such teaching or suggestion.

Accordingly, for at least the above reasons, the subject rejection should be withdrawn.

Claims 1-11, 42-48 and 57-63 stand rejected under 35 U.S.C. 103(a) "as being unpatentable over Bennett et al ((J. Chem. Soc. (C), 1970, page 2049-2051), and Chen et al (Biotechnology Letters, volume 14 No. 4 (April 1992) pp. 269-274) in view of Milstein et al (The Journal of Biological Chemistry, Vol. 250, No. 12, Issue of June 25, pp. 4782-4785, 1975)." In support of the rejection, the Patent Office states the following:

> The instant claims are directed to various deuterated catecholamine derivatives of the general formula I. Further, pharmaceutical compositions containing deuterated catecholamine derivatives are embodied in the instant application.
>
> Determination of Scope and content of the Prior Art (MPEP § 2141.01)
>
> Bennett et al teach deuterated 3,4 dihydroxy phenylalanine (β-deuterated amino acid) (see column 1, 2nd para, page 2050, J. Chem. Soc. (C), 1970, page 2049-2051) and Chen et al teach preparation of optically pure [α-^2H]-α-amino acids (α-deuterated amino acids) (see page Scheme I, page 270, Biotechnology Letters, volume 14 No. 4 (April 1992) pp. 269-274) and further Milstein et al teach 2,3,4,5,6-pentadeutero-Lphenylalanine (see column 1 page 4783, para. 3, The Journal of Biological Chemistry, Vol. 250, No. 12, Issue of June 25, pp. 4782-4785, 1975 and see the whole document).
>
> Ascertainment of the difference between the Prior Art and Claims (MPEP § 2141.02)
>
> The difference between the instant compounds and Bennett et al is that some of the instant compounds require deuteriation at the ring, and at α carbon. Bennett et al teaches the deuteriation of only at the β-carbon of the amino acid. Chen teaches the deuteriation at the α carbon and also at the ring but the reference is silent about the 3,4 dihydroxy groups. Milstein teaches studies on the phenylalanine

hydroxylase system in vivo. Milstein is silent about the deuterated catecholamine derivatives.

Finding of prima facie obviousness – rational and motivation (MPEP § 142-2143)

Accordingly, one of ordinary skill in the art would be motivated to prepare the instant compounds by modifying the substitutions around the core structure, since the dideuterated catecholamine derivative is anticipated. Substitution of the N-H or O-H or the carboxylic H with deuterium would have been obvious to one skilled in the art. The examiner contends that the combination of references is proper and an ordinary artisan would have had a reasonable expectation of success at the time of the instant invention to arrive at the instant compounds/compositions and hence it is prima facie [obvious].

Applicant respectfully traverses the subject rejection. As noted above, claim 1 has been amended in this paper to recite deuterated catecholamine derivatives of the general formula I in which, amongst other things, two deuterium atoms are located on the β-carbon and at least one of R^1, R^2, R^3 and R^4 is D. As acknowledged by the Patent Office, Bennett et al. is limited to teaching deuteration only at the β-carbon and not also at one or more of R^1, R^2, R^3 or R^4. The Patent Office attempts to cure this shortcoming in Bennett et al. by reference to Chen et al. and to Milstien et al. However, Applicant respectfully submits that one of ordinary skill in the art would have had no reason to combine the teachings of these three references in the manner proposed by the Patent Office. Chen et al. is limited to α-deuterated amino acids and would have provided no motivation to one of ordinary skill in the art to have substituted deuterium atoms on **both the α-carbon and the β-carbon**. Similarly, Milstien et al. is limited to ring-deuterated amino acids and would have provided no motivation to one of ordinary skill in the art to have substituted deuterium atoms on **both the β-carbon and the ring**.

As another factor demonstrating nonobviousness, Applicant wishes to note that Bennett was published in 1970, Milstien was published in 1975, and Chen was published in 1992. This means that, over a 22-year-period of research relating to deuterated L-phenylalanine derivatives, nobody had the idea to combine the teachings of these references in the manner proposed by the Patent Office. Moreover, the present application was filed in 2003, i.e., another 11 years after Chen was published in 1992. There was no need in the past to combine these publications because the effect of deuteration on L-DOPA was not the focus of those of ordinary skill in the art. By contrast, the present inventor has found that there is a great pharmacological effect and that this effect depends on the position of the deuteration. Furthermore, the present inventor has disclosed the teaching that these deuterated compounds are useful in the treatment of illnesses. Because these documents do not teach any medical use, it is believed that it was not obvious to combine the teaching of the cited documents.

Furthermore, the experiments below support the nonobviousness of the claimed compounds over the compounds of the references:

Locomotor activity measurements in reserpine treated rats.

Locomotor activity following administration of L-DOPA (L-2-amino-3-(3,4-dihydroxyphenyl) propionate) and alpha,beta,beta-D3-L-DOPA (L-2-amino-2,3,3-trideutero-3-(3,4-dihydroxyphenyl) propionate) was measured in reserpine treated rats. The night before experiments, rats were pre-treated with reserpine (5 mg/kg i.p.) or vehicle. 10-12 hours later, locomotor

experiments were performed. In order to prevent peripheral degradation of L-DOPA and alpha,beta,beta-D3-L-DOPA, the peripheral decarboxylase inhibitor carbidopa (10 mg/kg i.p.) was administered 30 minutes before administration of any of the L-DOPA compounds. Animals were then injected with the test compounds (200 mg/kg i.p.) and locomotor activity measurements begun 10 minutes later. Rats were placed in light attenuating boxes with infrared beams in two planes along the walls and each beam interruption resulting from the animal's movements was recorded by a computer.

The behavioural experiments demonstrated that alpha,beta,beta-D3-L-DOPA increases locomotor activity in reserpine-treated rats significantly more than L-DOPA (Fig.1).

Microdialysis experiments in rats

The output of dopamine in the striatum of male Wistar rats was measured following administration of 50 mg/kg i.p. of L-DOPA (L-2-amino-3-(3,4-dihydroxyphenyl) propionate), beta,beta-D2-L-DOPA (L-2amino-3,3-dideutero-3-(3,4-dihydroxyphenyl)propionate) and alpha,beta,beta-D3-L-DOPA (L-2-amino-2,3,3-trideutero-3-(3,4-dihydroxyphenyl) propionate). Rats were anaesthetized and mounted in a stereotaxic frame. Dialysis probes were implanted in the dorsolateral striatum (AP: +0.6: ML + 3.0: DV -6.2 relative to bregma and the dural surface according to the atlas of Paxinos and Watson (1998)). Dialysis experiments were conducted approximately 48 h after surgery in freely moving rats. The dialysis probe was perfused with a physiological perfusion solution at a rate of 2.5µl/min set by a microinfusion pump. Dialysate was

collected over 15 min intervals and automatically injected into a high performance liquid chromatography (HPLC) system. On-line quantification of dopamine in the dialysate was accomplished by electrochemical detection (ESA, Chelmsford, MA). Dopamine levels were expressed and statistically analyzed as percent of basal levels. The location of microdialysis probes was verified in slices of formalin-fixed tissue stained with neutral red.

The microdialysis experiments in rats demonstrated that administration of alpha,beta,beta-D3-L-DOPA (50 mg/kg, i.p.) increases dopamine output in the striatum significantly more than L-DOPA or D2-L-DOPA (Fig.2). In addition, it can be seen that the pharmacological effect of D2-L-DOPA is even lower than that of the naturally occurring L-DOPA.

Fig. 1 Locomotion activity measurements in reserpine treated rats after administration of L-DOPA and alpha,beta,beta-D3-L-DOPA

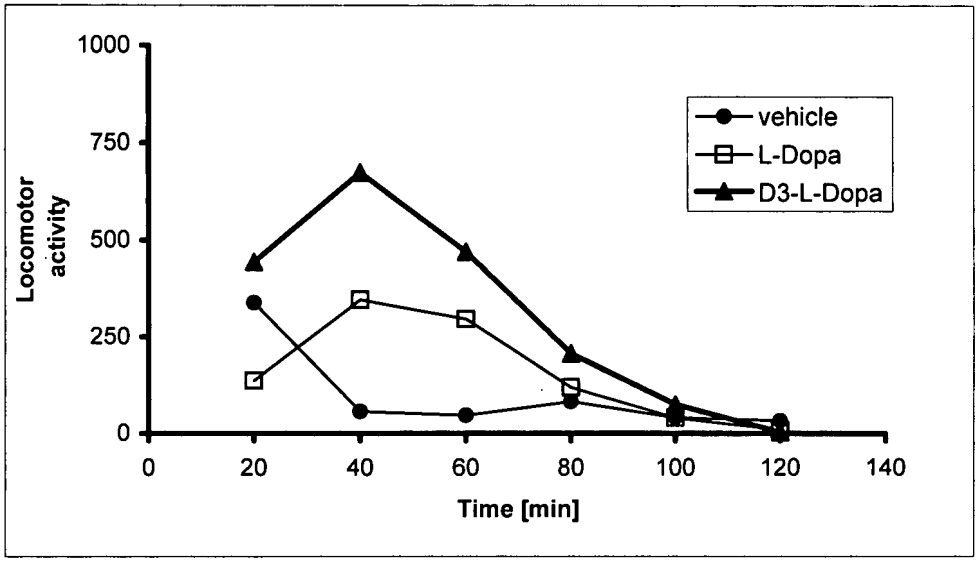
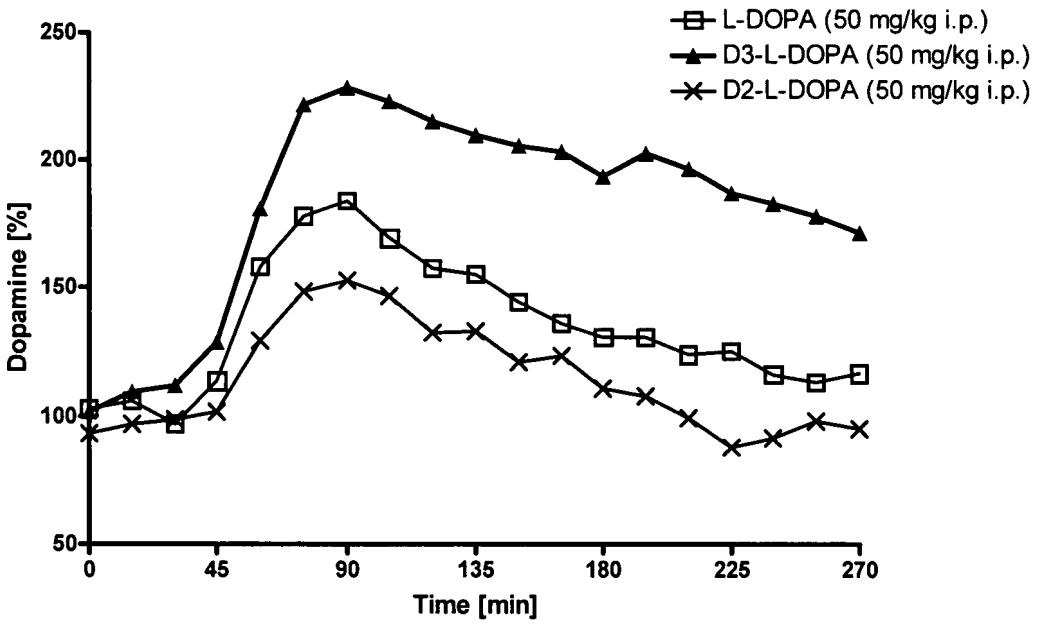


Fig.2 Output of dopamine in the stratum after administration of L-DOPA and alpha,beta,beta-D3-L-DOPA



Accordingly, for at least the above reasons, the subject rejection should be withdrawn.

Applicant notes that claims 34-41 and 49-55 have not been rejected on the basis of prior art. Therefore, in view of the fact that Applicant has overcome the non-art rejections in the outstanding Office Action, Applicant respectfully submits that claims 34-41 and 49-55 should be allowed immediately.

In conclusion, it is respectfully submitted that the present application is now in condition for allowance. Prompt and favorable action is earnestly solicited.

If there are any fees due in connection with the filing of this paper that are not accounted for, the Examiner is authorized to charge the fees to our Deposit Account No. 11-1755. If a fee is

required for an extension of time under 37 C.F.R. 1.136 that is not accounted for already, such an extension of time is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

Kriegsman & Kriegsman

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Dated: June 15, 2007

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on June 15, 2007.

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Reg. No. 33,529
Dated: June 15, 2007